Enablement Rejections

At page 2 of the Office Action, the Examiner rejected claims 11 and 21 as nonenabled. In making the rejection, the Examiner asserted that the specification does "not provid[e] sufficient teaching on deregulating the KAPPA-to-DAPA biosynthetic step." (Office Action, p. 2). The Examiner asserts that one of ordinary skill in the art would not be able to make and use the claimed invention without the DNA sequences of the specific cassettes, i.e., P_{15}*bio*, or the deposit of those strains. *Id.* at 3.

To the extent understood, it is believed that this basis of rejection was addressed in the prior Response. In particular, we noted that strain BI282 is a deposited strain that contains a P_{15} *bio* cassette amplified at the *bio* locus. (*See* Specification, p. 13). We respectfully refer the Examiner to pages 3-4 of the June 1, 1999 RESPONSE TO OFFICE ACTION INCLUDING AMENDMENT, which notes that strain BI282 was deposited with the American Type Tissue Culture Collection ("ATCC") in Rockville, Maryland, under the requirements of the Budapest Treaty. In that same paper, at page 25, the instant specification was amended to reflect this fact.

Thus, with the deposit of BI282, one of skill in the art would be able to obtain and use a bacterium with a deregulated KAPA-to-DAPA biosynthetic pathway. To the extent the Examiner appears to not have considered the above, reconsideration and withdrawal of the rejection is requested.

The Examiner has also rejected claims 9, 10, and 13-22 under 35 USC § 112, first paragraph, as containing subject matter that is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner requires proof of deposit of "bacterium resistant to S-2-aminoethyl-L-cysteine" ("AEC") and "bacterium engineered to produce a SAM-utilizing DAPA aminotransferase."

The Examiner is directed to page 25 of the specification. Therein, a table lists several culture deposits that were made at the ATCC, under the requirements of the Budapest Treaty. The Examiner's attention is particularly directed to strains BI 641 (ATCC No. 202002) and BI 642 (ATCC No. 202001), which are "bacterium resistant to AEC." *See*, for example, page 23, line 28 to page 24, line 8 and page 25, lines 24 and 25. We also refer the Examiner to strain BI 96 (ATCC NO. 202000), which is a "bacterium engineered to produce a SAM-utilizing DAPA aminotransferase." *See*, for example, page 19, line 27 to page 20, line 31 and page 25, line 19. In addition, it is noted that beginning on page 24, line 16, there is a "Deposit Statement" regarding the deposit, *inter alia*, of the above strains. Thus, for the foregoing reasons, it is submitted that the rejection cannot stand and should be withdrawn.

Anticipation Rejection

Claims 1, 2, 6, 7, and 12 were rejected under 35 USC § 102(b) as being anticipated by Levy-Schil et al. ("Levy-Schil"). See Office Action at page 4. Reconsideration and withdrawal of the rejection are requested for the following reasons.

Levy-Schil discloses the construction and characterization of *E. coli* strains overexpressing homologous *bio* genes. p. 756. SAM was disclosed as being the amino donor in the conversion of KAPA-to-DAPA in *E. coli*. Figure 1. In culturing cells for gene expression, 1 μg/ml of vitamin-free casamino acids were disclosed as supplementing the M9 glucose medium. p. 756. Further, for biotin quantification, the cells were grown overnight in M9 glucose medium supplemented with an unknown quantity of vitamin-free casamino acids. *Id.*

In making the rejection, the Examiner asserted that Levy-Schil disclosed "a method of making biotin by culturing *E. coli* in a medium comprising casamino acids and purifying the biotin produced." (Office Action, p. 4). The Examiner reasons that since

"casamino acids comprise lysine and aspartate, as lysine precursor," Levy-Schil necessarily anticipates claims 1, 2, 6, 7, and 12. *Id.*

The Examiner has not even alleged, much less shown with the requisite specificity, that Levy-Schil discloses any process that employs a microorganism containing a "lysine-utilizing DAPA amino transferase," a limitation that is affirmatively cited in claims 1, 6, 7, and 12. In fact, Levy-Schil discloses **only** a SAM-utilizing DAPA amino transferase. *See* Fig. 1.

Anticipation under 35 USC § 102(b) requires disclosure in a single reference of **every element** of the claimed invention, and the Examiner **must** identify wherein **each and every** facet of the claims invention is disclosed in the cited reference. *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). Having failed to establish anticipation, the rejection cannot stand and should be withdrawn.

In addition, there is no disclosure in Levy-Schil of a process for culturing a bacterium that involves lysine, a lysine analog, or a lysine precursor being exogenously added to the culture and totals at least 10 mmoles per liter of culture, a limitation that is now affirmatively recited in claim 1, thus, for this additional reason, the rejection should be withdrawn.

Obviousness Rejection

The Examiner has set forth two rejections under 35 U.S.C. § 103(a). First, the Examiner has rejected claims 1 and 8 under 35 USC § 103(a) as being unpatentable over Levy-Schil in view of Yamada et al. (US Patent No. 4,563,426) ("Yamada"). Second, the Examiner has rejected claims 1, 9, and 10 under 35 USC § 103(a) as being unpatentable over Levy-Schil in view of Komatsubara et al. (US Patent No. 5,374,554) ("Komatsubara").

The disclosure in Levy-Schil has been discussed above and is incorporated herein by reference.

Yamada discloses a process for cultivating "a microorganism having the ability to produce a biotin-vitamer in a culture medium in the presence of a biotin-vitamer precursor to produce the biotin-vitamer and accumulate it in the culture medium." Col. 1, lns. 23-30. The biotin-vitamer precursor is "added to the culture medium after the microbial cells have grown." Col. 1, lns. 30-32. The biotin-vitamer produced by the disclosed process "consists mainly of dethiobiotin, biotin, and biotin sulf-oxide." Col. 1, lns. 33-35. Biotin-vitamer precursors are "a precursor of the desire biotin-vitamer," e.g., pimelix acid, azelaic acid, and desthiobiotin. Col. 58-66. Nitrogen sources in the culture medium include, *inter alia*, casamino acids and amino acids. Col. 2, lns. 4-9.

In rejecting claims 1 and 8, the Examiner asserted that it would have been obvious "to convert the desthibiotin produced as taught in Levy-Schil, into biotin as taught by Yamada," because "one of ordinary skill in the art is motivated to combine the teachings." (Office Action, p. 6). The Examiner reasoned that there would have been a "reasonable expectation of success" to use Levy-Schil's dethiobiotin in Yamada's process for producing biotin. *Id.*

The Examiner did not even allege, much less provide any factual support for, that the process of Yamada employs a microorganism containing a lysine-utilizing DAPA aminotransferase, as recited in all claims. Thus, one of ordinary skill in the art, proceeding in the allegedly obvious manner suggested by the Examiner, would not end up with the claimed subject matter. Since the posited use of Levy-Schil desthiobiotinn in Yamada's process "falls short" of what is claimed, the rejection is fundamentally deficient and must be withdrawn. *Uniroyal, Inc. v. Rudkin-Wiley, Corp.*, 5 USPQ2d 1434, 1439 (Fed. Cir. 1988); *Ex parte* Levy, 17 USPQ2d at 1465.

Furthermore, also missing from the Examiner's reasoning is any assertion, much less a demonstration, that the culture in the Yamada process contains lysine, a lysine analog, or a lysine precursor that is exogenously added to the culture and totals at least 10 mmols per liter of culture, as now required in claim 1. Thus, for this additional reason, the posited combination falls short and the rejection must be reversed.

Claims 1, 9, and 10 were rejected under 35 USC § 103(a) of as being unpatentable over Levy-Schil in view of Komatsubara at page 6.

The disclosure in Levy-Schil has been discussed above and is incorporated herein by reference.

Komatsubara discloses producing biotin by cultivating a microorganism containing a biotin gene cloned from a microorganism of the genus *Serratia*. Col. 1, lns. 56-68. Preferable species of *Serratia* have resistance to, inter alia, lysine analogs, such as S-aminoethylcysteine. Col. 3, lns. 30-44. Cultivation of the microorganism takes place in a conventional medium wherein the microorganism can grow. Col. 5, lns. 59-61.

In making the rejection, the Examiner asserted that it would have been obvious "to produce biotin using the *Serratia* strain resistant to S-2-aminoethyl-L-cysteine as taught by Komatsubara using the growth media taught by Levy-Schil." (Offcie Action, pp. 6-7).

The Examiner fails to even allege, much less provide any factual support, that the *Serratia* strain used in the Komatsubara process is a microorganism containing a lysine-utilizing DAPA aminotransferase, as recited in all claims. Once again, one of ordinary skill in the art, proceeding in the allegedly obvious manner suggested by the Examiner, would not end up with the claimed subject matter. Since the posited use of Levy-Schil desthiobin in the Komatsubara process "falls short" of what is claimed, the rejection is fundamentally deficient and must be withdrawn. *Uniroyal, Inc. v. Rudkin-Wiley, Corp.*, 5 USPQ2d 1434, 1439 (Fed. Cir. 1988); *Ex parte* Levy, 17 USPQ2d at 1465.

Furthermore, with regard to dependent claims 9 and 10, which recite that the microorganism has "resistance to a lysine analog," and that the "analog is AEC," respectively, the Examiner has not alleged, much less demonstrated, that the Komatsubara strain has the phenotypic properties recited in the claims. Again, the posited combination is **not** what is claimed.

Finally, as amended, claim 1 now recites that lysine, a lysine analog, or a lysine precursor is exogenously added to the culture and totals at least 10 mmoles per liter of culture. Also missing from the Examiner's reasoning is any assertion, much less a demonstration, that the culture in the Komatsubara process have at least 10 mmols per liter of exogenously added lysine, a lysine analog, or a lysine precursor and totals at least 10 mmoles per liter of culture, as required in all claims. Thus, for this additional reason, the posited combination falls short and the rejection must be reversed.

Obviousness must be based on facts. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993), *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970) ("Cold, hard facts"). When, as here, the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and cannot stand. *In re Deuel*, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). Thus, for the foregoing reasons, reconsideration and withdrawal of the rejections is respectfully requested.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on December 17, 1999.

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Respectfully submitted,

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